A dendritic iron porphyrin as a novel haemoprotein mimic: effects of the dendrimer cage on dioxygen-binding activity

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An iron(II) porphyrin 1-methylimidazole (mim) complex covalently encapsulated within a large aryl ether dendritic cage, $Fe^{II}(mim)_2L^5$, displays reversible dioxygen-binding activity, in which the dioxygen adduct survives over a period of months even in the presence of water, and exhibits a half-life of 50 h upon exposure to carbon monoxide.

In mimicking biological functions of haemoproteins, one of the attractive targets is to realize the reversible dioxygen-binding activities of haemoglobin and myoglobin. However, (1) μ -oxo dimer formation and/or (2) H⁺ (H₂O)-driven autoxidation (Scheme 1) obstruct the reversibility of this process. In order to thwart μ -oxo dimer formation, a variety of sterically hindered iron porphyrins have been synthesized,¹ some of which form stable dioxygen adducts under anhydrous conditions.² On the other hand, in aqueous media, successful examples have been limited to only an iron picket-fence porphyrin embedded within a synthetic bilayer membrane.³ Herein we report an iron porphyrin covalently encapsulated within a large aryl ether dendrimer cage as the first monomolecular model of dioxygen-carrying haemoproteins.

Dendrimers are globular-shaped, hyper-branched macromolecules of nanoscopic size.⁴ Recently, we have synthesized the first dendritic porphyrins (H₂L^{*n*}, n = 1-5; the number of aryloxy layers),⁵⁻⁷ in which the porphyrin functionality is attached to four aryl ether dendritic arrays.⁸ ¹H NMR studies showed an egg-like structural resemblance to higher-generation H₂L^{*n*} (n = 4, 5),⁶ namely, a non-constrained interior environment encapsulated by a stiff exterior shell. For the preparation of Fe^{III}ClL^{*n*} (n = 1, 3-5) (Fig. 1), the free-base H₂L^{*n*} and FeBr₂ (2–10 equiv.) were refluxed in thf for 18 h, and the reaction mixture was chromatographed on silica gel with CHCl₃ as eluent, where the second band collected was poured into



Scheme 1 Irreversible oxidation pathways for iron porphyrin-dioxygen adducts; por = porphyrinate, B = base



Fig. 1 Schematic representations of $\text{Fe}^{\text{III}}L^n\text{Cl}$ (n = 1, 3-5)

methanolic HCl (0.1 mol dm⁻³). Fe^{III}ClL^{*n*} (n = 1, 3-5), thus obtained as precipitates, were reduced with Na₂S₂O₄ (1.5 equiv.) in toluene–water under argon, and the separated organic layer was washed with deaerated water, dried over Na₂SO₄, and evaporated to dryness, leaving Fe^{II}L^{*n*} in 95% (n = 1)–65% (n = 5) yields based on H₂L^{*n*}.

The dioxygen-binding activities of the Fe^{II}Lⁿ (n = 1, 3-5) family were investigated in anhydrous or water-saturated toluene $(4 \times 10^{-3} \text{ dm}^3)$ {[Fe^{II}Lⁿ]₀ = 2 × 10⁻⁵ mol dm⁻³} at 23 °C in the presence of 30 equiv. 1-methylimidazole (mim).† The reaction was monitored by means of electronic absorption spectroscopy, using a quartz cell of 1 mm pathlength connected to a round bottomed flask $(1 \times 10^{-2} \text{ dm}^3)$ with a three-way stopcock and a gas inlet regulator.[‡] As expected from previous work,^{1,9} the smallest complex, $Fe^{II}(min)_2L^1$ without any steric protection around the active site was instantly and irreversibly oxidized, upon introduction of O_2 , to give a μ -oxo dimer (422, 575 nm).¹ On the other hand, the larger $Fe^{II}(mim)_2L^n$ members of the family (n = 3-5) did not show any sign of μ -oxo dimer formation, and exhibited reversible dioxygen-binding profiles. An example is shown by the largest member, $Fe^{II}(O_2)(mim)L^5$ (Fig. 2) in anhydrous toluene, where the characteristic ab-sorbances at 423.5 and 548.5 nm did not decrease at all throughout observation over a period of 2 months in an atmospheric pressure of O2. When O2 was flushed out from the system by bubbling of N2, the dioxygen adduct changed back into the deoxygenated form. Such an oxygenation-deoxygenation cycle could be repeated many times without irreversible oxidation. Interestingly, reversible dioxygen uptake of FeII(mim)₂L⁵ was also observed in water-saturated toluene $\{[H_2O]_0: [Fe^{II}(mim)_2L^5]_0 = 1000: 1\}, ^{10}$ where the dioxygen adduct still showed an extremely long lifetime (Fig. 3, with 95%



Fig. 2 Structure of Fe^{II}(O₂)(mim)L⁵

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survival after 2 months) and a rate constant of decay (k_{decay}) of 7.4 × 10⁻¹³ s⁻¹. In contrast, smaller Fe^{II}(O₂)(mim)Lⁿ (n = 3, 4) showed rapid spectral changes as a result of irreversible autoxidation,¹¹ where the half-lives of the dioxygen adducts were 1.5 ($k_{decay} = 1.3 \times 10^{-4} \text{ s}^{-1}$) and 6 h (3.2 × 10⁻⁵ s⁻¹), respectively. Therefore, the large dendrimer cage of Fe^{II}(O₂)-(mim)L⁵ not only inhibits bimolecular oxidation but also provides a hydrophobic barrier around the active site preventing entry of water molecules.

Another interesting aspect is the low gas permeability through a large dendrimer framework. When O_2 was introduced into an anhydrous toluene solution (4 × 10⁻³ dm³) of the highest-generation complex Fe^{II}(mim)₂L⁵ (2 × 10⁻⁵



Fig. 3 % Survival of $\text{Fe}^{II}(O_2)(\min)L^n$ (n = 3-5), as determined from spectral changes in the Q-band region, in water-saturated toluene (4×10^{-3} dm³) at 23 °C in an atmospheric pressure of O₂; $[\text{Fe}^{II}L^n]_0 = 2 \times 10^{-5}$ mol dm⁻³, $[\text{Fe}^{II}L^n]_0$: $[\text{Imin}]_0$: $[\text{H}_2O]_0 = 1:30:1000$



Fig. 4 Reactions of (a) $Fe(min)_2L^n$ (n = 3, 5) with O_2 and (b) $Fe^{II}(O_2)(min)L^n$ (n = 3, 5) with CO in anhydrous toluene (4 × 10⁻³ dm³) under an atmospheric presure at 23 °C; $[Fe^{II}L^n]_0 = 2 \times 10^{-5}$ mol dm⁻³, $[mim]_0 = 6 \times 10^{-4}$ mol dm⁻³: time-conversion relationships, as determined from the spectral changes at the Soret region, upon bubbling of O_2 and CO, respectively, at a flow rate of 2.5×10^{-2} dm³ min⁻¹

mol dm⁻³), complete dioxygen binding required 12 min [Fig. 4(a)]. Bubbling N₂ into this system resulted in complete deoxygenation after 180 min. In sharp contrast, lower-generation Fe^{II}(mim)₂L³ required only 2 and 30 min for complete oxygenation and deoxygenation, respectively. These observations indicate that even small gaseous molecules such as O2 and N₂ find it difficult to permeate through the tightly packed dendrimer framework. Along such lines, even more interesting is the unusually high resistivity of $Fe^{II}(O_2)(mim)L^5$ towards carbonylation in a carbon monoxide atmosphere: upon introduction of CO into an anhydrous toluene solution, the dioxygen adduct was transformed only very slowly into the corresponding CO adduct (426, 548 nm)¹² at a rate constant $(k_{\rm CO})$ of 3.9 \times 10⁻⁶ s⁻¹, the half-life of the dioxygen adduct being as high as 50 h [Fig. 4(b)]. This is again in sharp contrast with lower-generation $Fe^{II}(O_2)(mim)L^3$ which was completely carbonylated within 30 min ($\tilde{k}_{CO} = 3.9 \times 10^{-4} \text{ s}^{-1}$).

In conclusion, we have exploited the first dendrimer-based monomolecular model of haemoproteins, which affords a longlived dioxygen adduct due to steric and hydrophobic protection of the active site. Restricted gas permeation through the dendrimer framework indicates a new potential of cascade architectures in materials science.

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Footnotes

† The complete formation of $Fe^{II}(mim)_2L^n$ (n = 3-5) at $[mim]_0/[Fe^{II}L^n]_0 = 30:1$ was confirmed by spectroscopic titration and S-shaped magnetic circular dichroism (MCD) bands in the Soret region, typical of low-spin six-coordinated iron(II) porphyrins.

‡ All gases were passed through a toluene bubbler before introduction to the reaction mixture in order to avoid vaporization of the solvent. The flow rate was adjusted at 2.5×10^{-2} dm³ min⁻¹ in each case.

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